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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/767,752	01/29/2004	Carol A. Tosaya	D-02017B1	5700
7590 David W. Collins Intellectual Property Law Suite 100 512 E. Whitehouse Canyon Road Green Valley, AZ 85614			EXAMINER KISH, JAMES M	
			ART UNIT 3737	PAPER NUMBER
			MAIL DATE 04/14/2009	DELIVERY MODE PAPER

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

<b>Office Action Summary</b>	<b>Application No.</b> 10/767,752	<b>Applicant(s)</b> TOSAYA ET AL.	
	<b>Examiner</b> JAMES KISH	<b>Art Unit</b> 3737	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

#### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

#### Status

- 1) ☒ Responsive to communication(s) filed on 22 December 2008.
- 2a) ☐ This action is **FINAL**.                      2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

#### Disposition of Claims

- 4) ☒ Claim(s) 1-6,9-11,14-21,23-38,40-48,50-56 and 58-103 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1-6,9-11,14-21,23-38,40-48,50-56 and 58-103 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

#### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

#### Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All    b) ☐ Some \*    c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

#### Attachment(s)

- |  |   |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)                                | 4) <input type="checkbox"/> Interview Summary (PTO-413)<br>Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)                       | 5) <input type="checkbox"/> Notice of Informal Patent Application                       |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)<br>Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____  |

## **DETAILED ACTION**

### ***Response to Arguments***

Applicant's arguments, filed December 22, 2008, with respect to the in view of Wallace has been fully considered and is persuasive. Therefore, the rejection has been withdrawn. However, upon further consideration, a new ground(s) of rejection is made as follows.

### ***Claim Objections***

Claims 5, 21, 24, 58, 75, 99 and 102 are objected to because of the following informalities:

Claim 5 is objected to because it is unclear whether "a shunt, a port, a dialysis filter, or other device" is intended to be positively claimed as part of the apparatus which the Applicant considers to be inventive.

Regarding claim 21, this claim recites functional language and does not provide, nor has any provision been shown previously, a structural aspect capable of producing this outcome. Claim 21 provides for how the emitter[s] function and/or operate as opposed to how it/they are arranged. Therefore, this claim is function and not structural.

Regarding claim 24(d), this claim recites functional language and does not provide, nor has any provision been shown previously, a structural aspect capable of producing this outcome. As the Applicant remarked, this portion of the claim recites what the emitter can emit." Therefore, it deals with how the emitter works operationally

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and does not change the structure of the device or the emitter itself. It is therefore function and not structure.

Claim 58 is objected to because "said system" at the last line of the claim lacks antecedent basis.

Claim 75 is objected to because it is unclear what is meant by "maintain, limit or control a temperature related to the... delivery of said acoustic, ultrasonic or vibratory energy." It is unclear what is portion of the apparatus is being maintained, limited or controlled in this option of claim 75.

Claim 99 is objected to because "the species, reactant, fragment or byproduct" of (b) is not fully inclusive of "a chemical or biological species, reactant, fragment, by-product or species related to the disease" as defined in (a).

Appropriate correction is required.

### ***Claim Rejections - 35 USC § 103***

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to

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consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 9, 11, 16-21, 25-32, 35-37, 42-43, 50-53, 54-56, 58-61, 63, 65-66, 71, 75-78, 81, 83-85 and 89 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bystritsky (US Patent No. 7,283,861) in view of any one of Thompson et al. (US Patent App. No. 2002/0072690) – herein referred to as Thompson – or Hardy et al. (US Patent No. 5,323,779) – herein referred to as Hardy – or Wuchinich (US Patent No. 4,526,571). Bystritsky discloses a system and corresponding method for modifying electrical currents in brain circuits through the simultaneous use of focused ultrasound pulse (FUP) and existing brain imaging systems. The invention is used for research treatment and diagnosis of neurological disorders whose biological mechanisms include brain circuits (see Abstract). Bystritsky's system utilizes a cap that fits on the head of a patient that comprises ultrasonic emitters for sending FUP into the patient's brain (see Figures 1-3). Among other disorders this can be used for are Parkinsonian Disease, Huntington Chorea, La Touretts and tick syndromes (column 1, lines 25-45). The FUP can be focused to any location(s) in the brain and can account for bone density and structure of the skull and brain (column 4, lines 25-34). Repeated use of the methods disclosed by Bystritsky can cause long-term or permanent changes to the [brain] circuits (column 4, lines 45-59). This can be used to aid in the recovery, growth, regrowth, new growth or improved physical, biological and cognitive functionality of brain-related or neurological-related cells, or functional pathways negatively impacted or stressed by

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deposits, nodules or bodies. The methods may be used without additional agents, but may also be used concurrently with pharmaceutical agents (column 5, lines 21-32). However, Bystritsky does not discuss a cooling system for the transducer or patient tissue.

Thompson teaches a cooling system and method (see Figures 10 and 11) that is used with a therapeutic ultrasound system. The cooling portion of the invention is described beginning at paragraph 83 and continues at least through paragraph 86.

Hardy teaches a heat surgery system monitored by real-time magnetic resonance temperature profiling in which the heating is caused by a pulsed, focused ultrasound transducer (see Abstract).

Wuchinich teaches an ultrasonic surgical device that is to be inserted into the patient. It is taught that devices that provide ultrasound that are inserted within a patient are known to have inlet and outlet conduits for supplying a circulating cooling fluid within the handpiece for removing excess heat (column 3, lines 39-41).

It would be obvious to one of ordinary skill in the art at the time the invention was made to incorporate a cooling system with the ultrasound therapy discussed by Gervais, as evidenced by any and all of Thompson, Hardy and/or Wuchinich – regardless of whether the transducer is external to the patient or internal to the patient - in order to remove excess heat from the transducer device because the excess heat could damage healthy tissue if in contact with such tissue, or even the patient's skin thereby causing unnecessary discomfort, or monitor the heat at the transducer for the same reasons, or monitor the patient tissue being treated for the same reasons.

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Regarding independent claim 1, portions (b), (c), and (e) are intended uses of the apparatus.

Regarding claims 29-31, these claims are method steps and do not limit the structure from which these claims ultimately dependent.

Regarding claim 36, the fact that acoustic or vibratory therapy exposure effects the action of the drug is not a structural limitation, but rather is a property based on the drug, medicament, vitamin, etc., that is given to the patient. Bystritsky is capable of enhancing the effects of certain drug, medicament, vitamin, etc., that would be given to the patient if the drugs are effected by ultrasound.

Claims 1-6, 9-11, 16-21, 26-38, 40-41, 44-47, 52-56, 58-61, 63, 65, 67-81, 83-84, 86-94, 96-103 are rejected under 35 U.S.C. 103(a) as being unpatentable over Jolesz et al. (US Patent No. 5,752,515) – herein referred to as Jolesz - in view of Chalifour et al. (US Patent App. 2004/0006092) – herein referred to as Chalifour – and further in view of any one of Thompson, Hardy and Wuchinich. Jolesz discloses a method and apparatus for treating neurological disorders by ultrasonic delivery of compounds through the blood-brain barrier (BBB). See column 3, lines 44-67. The ultrasound is applied through the skull itself via a phased array of transducers, a focused ultrasound transducer or a combination of ultrasound source and an acoustic lens, placed outside the skull (column 2, line 66 through column 3, line 37). The ultrasound can be focused electronically or mechanically (column 5, lines 33-41). Discussion of cavitation can be found throughout the reference, and particularly at column 5, line 64 through column 6,

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line 27. The invention allows for both continuous wave or burst (pulsed) mode operation (column 6, line 24). The device uses image-based localization of the region. Such images can be obtained on the devices described at column 6, lines 38-61. The effects of the skull bone are incorporated to allow the ultrasound to focus at a common location (column 7, lines 33-51). Jolesz does not explicitly state that one such disease to be treated is Alzheimer's or any other protein-related disease, however, Alzheimer's Disease (AD) is a neurological, mental and behavioral disorder, and a known protein-related disease and therefore is incorporated into the possible disorders that are treatable by Jolesz as disclosed at column 3, lines 60-67). Chalifour teaches a method of treating or preventing an amyloid-related disease in a subject comprising administering to the subject a therapeutic amount of an amidine compound. The compound is used to, among other things, at least prevent, slow or stop deterioration of cognitive function in a patient (paragraph 75). It would have been obvious to one having ordinary skill in the art at the time the invention was made to incorporate the compounds of Chalifour into the method and system of Jolesz to treat amyloid-related diseases. Furthermore, Chalifour teaches several methods to pass the compound through the BBB and it would be obvious to one of skill in the art to combine the teachings of Chalifour and Jolesz in order to provide a more accurate entry port for the compound through the barrier. However, neither Jolesz nor Chalifour discuss a cooling system for the transducer or patient tissue.



Thompson teaches a cooling system and method (see Figures 10 and 11) that is used with a therapeutic ultrasound system. The cooling portion of the invention is described beginning at paragraph 83 and continues at least through paragraph 86.

Hardy teaches a heat surgery system monitored by real-time magnetic resonance temperature profiling in which the heating is caused by a pulsed, focused ultrasound transducer (see Abstract).

Wuchinich teaches an ultrasonic surgical device that is to be inserted into the patient. It is taught that devices that provide ultrasound that are inserted within a patient are known to have inlet and outlet conduits for supplying a circulating cooling fluid within the handpiece for removing excess heat (column 3, lines 39-41).

It would be obvious to one of ordinary skill in the art at the time the invention was made to incorporate a cooling system with the ultrasound therapy discussed by Gervais, as evidenced by any and all of Thompson, Hardy and/or Wuchinich – regardless of whether the transducer is external to the patient or internal to the patient - in order to remove excess heat from the transducer device because the excess heat could damage healthy tissue if in contact with such tissue, or even the patient's skin thereby causing unnecessary discomfort, or monitor the heat at the transducer for the same reasons, or monitor the patient tissue being treated for the same reasons.

With respect to the specific limitation of the independent claims, Jolesz provides an ultrasound emitter that will provide acoustic energy to a localized portion of the BBB. Therefore, the energy will indirectly enter the brain or neurological region which has been, is or is expected to potentially be subject to the abnormal bodies. The ultrasound

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will be emitted with a desired characteristic, i.e. in a controlled manner. The compound of Chalifour will then at least prevent, slow or stop deterioration of cognitive function in a patient.

Regarding claim 4, Jolesz teaches opening of the blood-brain-barrier as described above. Therefore, the apparatus is capable of providing acoustically driven... perfusion (i.e., the uptake of certain drugs) in a bloodflow path (through, in and around the BBB)... the enhanced or initiated flow contributing to mass transport of a species in a direction useful for its natural or artificial removal from the body. Since the BBB is opened by the methods of Jolesz, it would allow compounds to enter, or in the obvious alternative, exit, through the BBB.

Regarding claim 5, the device of Jolesz is capable of being operated in cooperation with or in support of a device that is intended to clean or extract bodily fluids.

Regarding claim 6, the device of Jolesz is at least capable of providing for (g) it provides ultrasound-assisted drug therapy supportive of the slowing or stopping of a neurodegenerative disease.

Claims 1, 14-15, 18-21, 23-25, 46, 48, 52-53, 64, 66, 75, 82, 91-95, 98-103 are rejected under 35 U.S.C. 103(a) as being unpatentable over Briskin et al. (US Patent No. 6,464,680) – herein referred to as Briskin - in view of Chalifour and further in view of any one of Thompson, Hardy and Wuchinich. Briskin discloses a method of enhancing cellular absorption of a substance delivered into a target region with the use

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of vibrational energy to the target region (see Abstract). The invention can be used in treatment of abnormalities of the brain (column 12, lines 4-14) by allowing treatment to brain cells protected by the blood-brain barrier (column 1, lines 54-55). In one embodiment, an injection needle and the ultrasound energy emitter are located on the end of a catheter and can be introduced through a blood vessel or other luminal cavity (column 3, lines 4-28). The ultrasound conditions induce a preferred cellular response that increases porosity and subsequent uptake of therapeutic agents (column 5, line 55 through column 6, line 8). See column 7, lines 43-55 for possible effects of drugs. The wave may be divergent or focused on a small spot with the resolution of the ultrasonic emitter device (column 9, lines 65-67 and column 11, lines 54-63). Column 5, lines 38-54 discuss the thermal index of the vasculature immediately around the device. It is monitored based on the equation found at line 43. Chalifour teaches a method of treating or preventing an amyloid-related disease in a subject comprising administering to the subject a therapeutic amount of an amidine compound. The compound is used to, among other things, at least prevent, slow or stop deterioration of cognitive function in a patient (paragraph 75). It would have been obvious to one having ordinary skill in the art at the time the invention was made to incorporate the compounds of Chalifour into the method and system of Briskin to treat amyloid-related diseases. Furthermore, Chalifour teaches several methods to pass the compound through the BBB and it would be obvious to one of skill in the art to combine the teaches of Chalifour and Briskin in order to provide a more accurate entry port for the compound through the barrier.

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However, neither Briskin nor Chalifour discuss a cooling system for the transducer or patient tissue.

Thompson teaches a cooling system and method (see Figures 10 and 11) that is used with a therapeutic ultrasound system. The cooling portion of the invention is described beginning at paragraph 83 and continues at least through paragraph 86.

Hardy teaches a heat surgery system monitored by real-time magnetic resonance temperature profiling in which the heating is caused by a pulsed, focused ultrasound transducer (see Abstract).

Wuchinich teaches an ultrasonic surgical device that is to be inserted into the patient. It is taught that devices that provide ultrasound that are inserted within a patient are known to have inlet and outlet conduits for supplying a circulating cooling fluid within the handpiece for removing excess heat (column 3, lines 39-41).

It would be obvious to one of ordinary skill in the art at the time the invention was made to incorporate a cooling system with the ultrasound therapy discussed by Gervais, as evidenced by any and all of Thompson, Hardy and/or Wuchinich – regardless of whether the transducer is external to the patient or internal to the patient - in order to remove excess heat from the transducer device because the excess heat could damage healthy tissue if in contact with such tissue, or even the patient's skin thereby causing unnecessary discomfort, or monitor the heat at the transducer for the same reasons, or monitor the patient tissue being treated for the same reasons.

Claims 42-43 and 62 are rejected under 35 U.S.C. 103(a) as being unpatentable over Jolesz in view of Hynynen et al (US Patent No. 6,514,221) – herein referred to as Hynynen - and further in view of Chalifour, even further in view of any one of Thompson, Hardy and Wuchinich. Jolesz discloses a method and apparatus for treating neurological disorders by ultrasonic delivery of compounds through the blood-brain barrier (BBB). However, while cavitation is discussed by Jolesz, the compounds delivered through the BBB are not explicitly cavitation aiding agents. Hynynen teaches a method of opening the blood-organ barrier of a subject providing an exogenous agent (see Abstract). The agent is described as having microbubbles or solid particles contained within that will vaporize via body heat or ultrasonic energy (see all of column 5, as well as column 6, lines 1-43). There is also a measure of the temperature elevation due to the sonication (column 9, line 65 through column 10, line 12). Hynynen also discusses non-focused ultrasound at column 10, lines 36-57. It would have been obvious to one having ordinary skill in the art at the time the invention was made to incorporate a cavitation inducing contrast agent as taught by Hynynen into the system of Jolesz in order to allow opening of the BBB at low enough energy levels so as not to induce thermal damage (see Abstract).

Chalifour teaches a method of treating or preventing an amyloid-related disease in a subject comprising administering to the subject a therapeutic amount of an amidine compound. The compound is used to, among other things, at least prevent, slow or stop deterioration of cognitive function in a patient (paragraph 75). It would have been obvious to one having ordinary skill in the art at the time the invention was made to

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incorporate the compounds of Chalifour into the method and system of Jolesz to treat amyloid-related diseases. Furthermore, Chalifour teaches several methods to pass the compound through the BBB and it would be obvious to one of skill in the art to combine the teaches of Chalifour and Jolesz in order to provide a more accurate entry port for the compound through the barrier. However, none of the above cited references discuss a cooling system for the transducer or patient tissue.

Thompson teaches a cooling system and method (see Figures 10 and 11) that is used with a therapeutic ultrasound system. The cooling portion of the invention is described beginning at paragraph 83 and continues at least through paragraph 86.

Hardy teaches a heat surgery system monitored by real-time magnetic resonance temperature profiling in which the heating is caused by a pulsed, focused ultrasound transducer (see Abstract).

Wuchinich teaches an ultrasonic surgical device that is to be inserted into the patient. It is taught that devices that provide ultrasound that are inserted within a patient are known to have inlet and outlet conduits for supplying a circulating cooling fluid within the handpiece for removing excess heat (column 3, lines 39-41).

It would be obvious to one of ordinary skill in the art at the time the invention was made to incorporate a cooling system with the ultrasound therapy discussed by Gervais, as evidenced by any and all of Thompson, Hardy and/or Wuchinich – regardless of whether the transducer is external to the patient or internal to the patient - in order to remove excess heat from the transducer device because the excess heat could damage healthy tissue if in contact with such tissue, or even the patient's skin thereby causing

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unnecessary discomfort, or monitor the heat at the transducer for the same reasons, or monitor the patient tissue being treated for the same reasons.

### ***Conclusion***

Any inquiry concerning this communication or earlier communications from the examiner should be directed to JAMES KISH whose telephone number is (571)272-5554. The examiner can normally be reached on 8:30 - 5:00 ~ Mon. - Fri..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brian Casler can be reached on 571-272-4956. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/BRIAN CASLER/  
Supervisory Patent Examiner, Art  
Unit 3737

JMK

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